



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: UCKUN ET AL. Examiner: UNKNOWN  
Serial No.: 10/612,215 Group Art Unit: UNKNOWN  
Filed: JULY 2, 2003 Docket: 12152.70USD1  
Due Date: OCTOBER 2, 2003  
Title: CATHEPSIN INHIBITORS IN CANCER TREATMENT

CERTIFICATE UNDER 37 CFR 1.8:

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail, with sufficient postage, in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on October 2, 2003.

By:  
Name:

*Kristin A. Wacek*  
*Kristin A. Wacek*

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

**23552**

PATENT TRADEMARK OFFICE

Sir:

We are transmitting herewith the attached:

- ☒ Transmittal Sheet in duplicate containing Certificate of Mailing
- ☒ Information Disclosure Statement, Form 1449, 1 Reference(s)
- ☒ Return postcard

Please consider this a PETITION FOR EXTENSION OF TIME for a sufficient number of months to enter these papers or any future reply, if appropriate. Please charge any additional fees or credit overpayment to Deposit Account No. 13-2725. A duplicate of this sheet is enclosed.

MERCHANT & GOULD P.C.  
P.O. Box 2903, Minneapolis, MN 55402-0903  
612.332.5300

By: *Anna M. Nelson*  
Name: Anna M. Nelson  
Reg. No.: 48,935  
ANelson:PSTkaw



N 10/612,215

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	UCKUN ET AL.	Examiner:	UNKNOWN
Serial No.:	10/612,215	Group Art Unit:	UNKNOWN
Filed:	JULY 2, 2003	Docket No.:	12152.70USD1
Title:	CATHEPSIN INHIBITORS IN CANCER TREATMENT		

CERTIFICATE UNDER 37 CFR 1.8:

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail, with sufficient postage, in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on October 2, 2003.

By:

Name:

*Kristine B. Wachen*  
*Kristine B. Wachen*

INFORMATION DISCLOSURE STATEMENT (37 C.F.R. § 1.97(b))

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

**23552**

PATENT TRADEMARK OFFICE

Dear Sir:

With regard to the above-identified application, the items of information listed on the enclosed Form 1449 are brought to the attention of the Examiner.

This statement should be considered because it is submitted within three months of the filing date of the above-identified application, which is not an application under 37 C.F.R. § 1.53(d). Accordingly, no fee is due for consideration of the items listed on the enclosed Form 1449.

In accordance with 37 C.F.R. § 1.98(a)(2) and § 1.98(d), copies have been provided only for those items listed on the enclosed Form 1449 that have not previously been cited by or submitted to the U.S. Patent and Trademark Office in parent application, U.S. Serial No. 09/539,739 filed on March 31, 2000 now U.S. Patent No. 6,605,589 B1.

No representation is made that a reference is "prior art" within the meaning of 35 U.S.C. §§ 102 and 103 and Applicants reserve the right, pursuant to 37 C.F.R. § 1.131 or otherwise, to establish that the reference(s) are not "prior art." Moreover, Applicants do not represent that a reference has been thoroughly reviewed or that any relevance of any portion of a reference is intended.

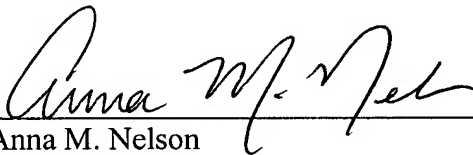
Consideration of the items listed is respectfully requested. Pursuant to the provisions of M.P.E.P. 609, it is requested that the Examiner return a copy of the attached Form 1449, marked as being considered and initialed by the Examiner, to the undersigned with the next official communication.

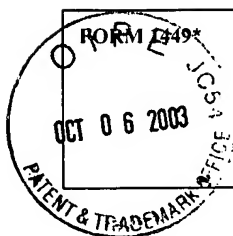
Please charge any additional fees or credit any overpayment to Deposit Account No. 13-2725.

Respectfully submitted,

MERCHANT & GOULD P.C.  
P.O. Box 2903  
Minneapolis, Minnesota 55402-0903  
(612) 332-5300

Date: October 2, 2003

  
\_\_\_\_\_  
Anna M. Nelson  
Reg. No. 48,935  
AMN:PSTkaw



## INFORMATION DISCLOSURE STATEMENT

## IN AN APPLICATION

(Use several sheets if necessary)

Docket Number:

12152.70USD1

Application Number:

10/612,215

Applicant: UCKUN ET AL.

Filing Date: 07/02/2003

Group Art Unit: UNKNOWN

## U.S. PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NO.	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	5,883,121	03/16/1999	Yamashita et al.			
	6,605,589 B1	08/12/2003	Uckun et al.			

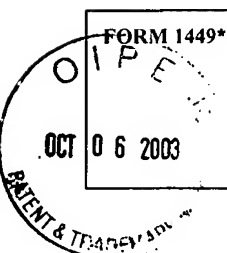
## FOREIGN PATENT DOCUMENTS

	DOCUMENT NO.	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
						YES	NO
	WO 98/49190	11/05/1998	PCT				
	WO 01/44464	06/21/2001	PCT				

## OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

	Andreason G. (1993) Electroporation As a Technique for the Transfer of Macromolecules into Mammalian Cell Lines. <i>J. Tiss. Cult. Meth.</i> , 15, 56-62
	Baldwin E, Bhat T, Gulnik S, Hosur M, Sowder II R, Cachau R, Collins J., Silva A, (1993). Crystal structures of native and inhibited forms of human cathepsin D: Implications for lysosomal targeting and drug design. <i>Proc. Natl. Acad. Sci.</i> , 90: 6796-6800
	Blandino GB, Levine AJ, Oren M (1999). Mutant p53 gain of function: differential effects of different p53 mutants on resistance of cultured cells to chemotherapy. <i>Oncogene</i> 18: 477-485.
	Brimmell M, Mendiola R, Mangion J, Packham G (1998). BAX frameshift mutations in cell lines derived from human haemopoietic malignancies are associated with resistance to apoptosis and microsatellite instability. <i>Oncogene</i> 16: 1803-1812.
	Chisholm V.. (1995). High efficiency gene transfer into mammalian cells. <i>DNA Cloning IV: A Practical Approach</i> , Mammalian Systems, Glover and Hanes, eds., pp 1-41
	Chow SC, Weiss M, Kass GE, Holmstrom TH, Eriksson JE, Orrenius S (1995). Involvement of multiple proteases during Fas-mediated apoptosis in T lymphocytes. <i>FEBS Lett</i> 364: 134-138.
	Cordone I, Masi S, Mauro FR, Soddu S, Morsilli O, Valentini T, Vegna ML, Guglielmi C, Mancini F, Guiliacci S, Sacchi A, Mandelli F, Foa R (1998). p53 Expressions in B-cell chronic lymphocytic leukemia: a marker of disease progression and poor prognosis. <i>Blood</i> 91: 4342-4349.
	Demuth HU, Schierhorn A, Bryan P, Hofke R, Kirschke H, and Bromme D (1996). N-peptidyl, O-acyl hydroxamates: comparison of the selective inhibition of serine and cysteine proteinases. <i>Biochim Biophys Acta</i> 1295: 179-186.
	Doman RK, Perez M, Donato NJ (1999). JNK and p53 stress signaling cascades are altered in MCF-7 cells resistant to tumor necrosis factor-mediated apoptosis. <i>J. Interferon Cytokine Res</i> 19: 261 - 269.
	Duffy MJ (1992). The role of proteolytic enzymes in cancer invasion and metastasis. <i>Clin Exp Metastasis</i> 10: 145-155.

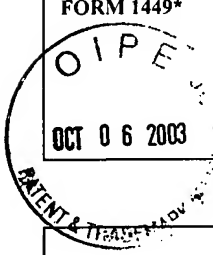
EXAMINER	DATE CONSIDERED
EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form for next communication to the Applicant.	



<b>FORM 1449*</b> <b>INFORMATION DISCLOSURE STATEMENT</b>  <b>IN AN APPLICATION</b> (Use several sheets if necessary)	Docket Number: 12152.70USD1	Application Number: 10/612,215
	Applicant: UCKUN ET AL.	
	Filing Date: 07/02/2003	Group Art Unit: UNKNOWN

	Fearnhead HO, Dinsdale D, Cohen GM (1995). An interleukin-1 beta-converting enzyme-like protease is a common mediator of apoptosis in thymocytes. <i>FEBS Lett</i> 375: 283-288.
	Friedrich B, Jung K, Lein M, Turk I, Rudolph B, Mampel G, Schnorr D, and Loening SA (1999). Cathepsin B,H, L and cysteine protease inhibitors in malignant prostate cell lines, primary cultured prostatic cells and prostatic tissue. <i>Eur J Cancer</i> 35: 138-144.
	Garcia-Calvo M, Peterson EP, Leiting B, Ruel R, Nicholson DW, Thornberry NA (1998). Inhibition of human caspases by peptide-based and macromolecular inhibitors. <i>J Biol Chem</i> 273: 32608-32613.
	Graham F, Van Der Eb A (1973). A New Technique for the Assay of Infectivity of Human Adenovirus 5 DNA. <i>Virology</i> , 52, 456-457
	Graham F, Prevec L, (1991). Manipulation of Adenovirus Vectors. <i>Gene Transfer and Expression Protocols</i> , pp 109-128,
	Green DR, Reed JC (1998). Mitochondria and apoptosis. <i>Science</i> 281: 1309-1312.
	Gutiérrez MI, Cherney B, Hussain A, Mostowski H, Tosato G, Magrath I, Bhatia K (1999). Bax is frequently compromised in Burkitt's lymphomas with irreversible resistance to Fas-induced apoptosis. <i>Cancer Res</i> 59: 696-703.
	Heidtmann HH, Salge U, Abrahamson M, Bencina M, Kastalic L, Kopitar-Jerala N, Turk V, and Lah TT (1997). Cathepsin B and cysteine protease inhibitors in human lung cancer cell lines. <i>Clin Exp Metastasis</i> 15: 368-381.
	Henkart PA (1996). ICE family protease: mediators of all apoptotic death? <i>Immunity</i> 4: 195-201.
	Isahara K, Ohsawa Y, Kanamori S, Shibata M, Waguri S, Sato N, Gotow T, Watanabe T, Momoi T, Urabe K, Kominami E, and Uchiyama Y (1999). Regulation of a novel pathway for cell death by lysosomal aspartic and cysteine proteases. <i>Neuroscience</i> 91: 233-249.
	Jones B, Roberts PJ, Faubion WA, Kominami E, and Gores GJ (1998). Cystatin A expression reduces bile salt - induced apoptosis in a rat hepatoma cell line. <i>Am J Physiol</i> 275: G723-730.
	Kao F, Puck T. (1968). Genetics of Somatic Mammalian Cells, VII. Induction and Isolation of Nutritional Mutants in Chinese Hamster Cells. <i>Proc. Natl. Acad. Sci. USA</i> , 60, 1275-1281
	Keppler D, Sameni M, Moin K, Mikkelsen T, Diglio C, and Sloane B (1996). Tumor progression and angiogenesis: cathepsin B & Co. <i>Biochem Cell Biol</i> 74: 799-810.
	Keyszer G, Heer A, Kriegsmann J, Geiler T, Trabandt A, Keysser M, Gay R, Gay S, (1995). Comparative Analysis of Cathepsin L, Cathepsin D, and Collagenase Messenger RNA Expression in Synovial Tissues of patients with rheumatoid arthritis and osteoarthritis, by in Situ Hybridization. <i>Arthritis Rheum.</i> , 38: 976-984
	Kos J. and Lah TT (1998). Cysteine proteinase and their endogenous inhibitors: Target proteins for prognosis, diagnosis and therapy in cancer (Review). <i>Oncol Rep</i> 5: 1349-1361.
	Krueger, S., Haeckel, C., Buehling, F., and Roessner, A. (1999) "Inhibitory Effects of Antisense Cathepsin B cDNA Transfection on Invasion and Motility in a Human Osteosarcoma Cell Line". <i>Cancer Research</i> , 59:6010-6014.
	Leto, G. et al., "Effects of E-64 (Cysteine-Proteinase Inhibitor) and Pepstatin (Aspartyl-Proteinase Inhibitor) on Metastasis Formation in Mice with Mammary and Ovarian Tumors," <i>In Vivo</i> , Vol. 8, pp. 231-236 (1994)

EXAMINER	DATE CONSIDERED
EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form for next communication to the Applicant.	

<b>FORM 1449*</b>  <b>INFORMATION DISCLOSURE STATEMENT</b>  <b>IN AN APPLICATION</b> (Use several sheets if necessary)	Docket Number: 12152.70USD1	Application Number: 10/612,215
	Applicant: UCKUN ET AL.	
	Filing Date: 07/02/2003	Group Art Unit: UNKNOWN

		Li P, Nijhawan D, Budihardjo I, Srinivasula SM, Ahmad M, Alnemri E, Wang X (1997). Cytochrome c and dATP-dependent formation of Apaf-1/caspase-9 complex initiates an apoptotic protease cascade. <i>Cell</i> 91: 479-489.
		Lowe SW, Ruley HE, Jacks T, Housman DE (1993). p53-dependent apoptosis modulates the cytotoxicity of anticancer agents. <i>Cell</i> 74: 957-967.
		Lowe SW, Schmitt EM, Smith SW, Osborne BA, Jacks T (1993b). p53 is required for radiation-induced apoptosis in mouse thymocytes. <i>Nature</i> 362: 847-849.
		Magi-Galluzzi C, Montironi R, Cangi MG, Wishnow K, Loda M (1998). Mitogen-activated protein kinases and apoptosis in PIN. <i>Virchows Arch</i> 432: 407-413.
		Makarewicz R, Drewa G, Szymanski W, and Skonieczna-Makarewicz I (1995). Cathepsin B in predicting the extent of the cervix carcinoma. <i>Neoplasia</i> 42: 21-24.
		Meijerink JP, Mensink EJ, Wang K, Sedlak TW, Sloetjes AW, de Witte T, Waksman G, Korsmeyer SJ (1998). Hematopoietic malignancies demonstrate loss-of-function mutations of BAX. <i>Blood</i> 91: 2991 - 2997.
		Memon SA, Moreno MB, Petrak D, Zacharchuk CM (1995). Bcl-2 blocks glucocorticoid - but not as Fas - or activation- induced apoptosis in a T cell hybridoma. <i>J Immunol</i> 155: 4644-4652.
		Mizuochi T, Yee S-T, Kasai M, Kakiuchi T, Muno D, Kominami E (1994). Both cathepsin B and cathepsin D are necessary for processing of ovalbumin as well as for degradation of class II MHC invariant chain. <i>Immunol. Lett.</i> , 43: 189-193
		Myers D, Jun X, Waddick K, Forsyth C, Chelstrom L, Gunther R, Tumer N, Bolen J, Uckun F. (1995). Membrane-associated CD19-LYN complex is an endogenous p53-independent and Bcl-2-independent regulator of apoptosis in human B-lineage lymphoma cells. <i>Proc. Natl. Acad. Sci. USA</i> , 92: 9575-9579
		Mort JS, and Buttle DJ. Cathepsin B (1997). <i>Int J Biochem Cell Biol</i> 29: 715-720.
		Peller S (1998). Clinical implications of p53: effect on prognosis, tumor progression and chemotherapy response. <i>Cancer Biol.</i> 8: 379-387.
		Pronk GJ, Ramer K, Amiri P, Williams LT (1996). Requirement of an ICE-like protease for induction of apoptosis and ceramide generation by REAPER. <i>Science</i> 271: 808-810.
		Roberts LR, Kurosawa H, Bronk SF, Fesmier PJ, Agellon LB, Leung W-Y, Mao F, and Gores GJ (1997). <i>Gastroenterology</i> 113: 1714-1726.
		Rooprai HK, and McCormick D (1997). Proteases and their inhibitors in human brain tumors: a review. <i>Anticancer Res</i> 17: 4151-4162.
		Sameni M, Elliott E, Ziegler G, Fortgens PH, Dennison C and Sloane BF (1995). Cathepsin B and cathepsin D are localized at the surface of human breast cancer cells. <i>Pathol Oncol Res</i> 1: 43-53.
		Schlegel J, Peters I, Orrenius S, Miller DK, Thornberry NA, Yamin TT, Nicholson DW (1996). CPP32/apopain is a key interleukin 1 beta converting enzyme-like protease involved in Fas-mediated apoptosis. <i>J Biol Chem</i> 271: 1841-1844.
		Shibata M, Kanamori S, Isahara K, Ohsawa Y, Konishi A, Kametaka S, Watanabe T, Ebisu S, Ishido K, Kominami E, and Uchiyama Y (1998). Participation of cathepsins B and D in apoptosis of PC12 cells following serum deprivation. <i>Biochem Biophys Res Commun</i> 251: 199-203.

EXAMINER	DATE CONSIDERED
EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form for next communication to the Applicant.	

FORM 1449* INFORMATION DISCLOSURE STATEMENT IN AN APPLICATION (Use several sheets if necessary)	Docket Number:	Application Number:
	12152.70USD1	10/612,215
	Applicant: UCKUN ET AL.	
	Filing Date: 07/02/2003	Group Art Unit: UNKNOWN

	Sivaparthi et al., "Expression of cathepsin D during the progression of human gliomas," <i>Neurosci Lett.</i> , Vol. 208, pp. 171-174 (1996)
	Slee EA, Zhu H, Chow SC, MacFarlane M, Nicholson DW, Cohen GM (1996). Benzyloxycarbonyl-Val-Ala-Asp (OMe) fluoromethylketone (Z-VAD.FMK) inhibits apoptosis by blocking the processing of CPP32. <i>Biochem J</i> 315: 21-24.
	Sloane BF, Moin F, Sameni M, Tait LR, Rozhin J, and Ziegler G (1994). Membrane-association of cathepsin B can be induced by transfection of human breast cells with c-Ha-ras oncogene. <i>J Cell Sci</i> 107: 373-384.
	Soderstrom, K-O. et al., "Expression of Acid Cysteine Proteinase Inhibitor (ACPI) in the Normal Human Prostate, Benign Prostatic Hyperplasia and Adenocarcinoma," <i>In. J. Cancer</i> , Vol. 62, pp. 1-4 (1995)
	Strohmaier AR, Porwol T, Acker H, and Spiess E (1997). Tomography of cells by confocal laser scanning microscopy and computer-assisted three-dimensional image reconstruction: localization of cathepsin B in tumor cells penetrating collagen gels <i>in vitro</i> . <i>J Histochem Cytochem</i> 45: 975-983.
	Summers M, Smith G (1987). A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures. <i>Texas Agriculture Experiment Station Bulletin</i> , 1555
	Thornberry NA, Lazebnik Y (1998). Caspases: enemies within. <i>Science</i> 281: 1312-1316.
	Uckun FM, Waddick KG, Mahajan S, Xiao J, Takata M, Bolen J, Kurosaki T (1996). BTK is a mediator of radiation-induced apoptosis in DT-40 lymphoma B cells. <i>Science</i> 273: 1096-1100.
	Vasilakos JP, Ghayur T, Carroll RT, Giegel DA, Saunders JM, Quintal L, Keane KM, Shivers BD (1995). IL-1 beta converting enzyme (ICE) is not required for apoptosis induced by lymphokine deprivation in an IL-2 dependent T cell line. <i>J Immunol</i> 155(7): 3433-3442.
	Weiss RE, Liu BC, Ahlering T, and Dubeau MJ (1990). Mechanism of human bladder tumor invasion: role of protease cathepsin B. <i>J Urol</i> 144: 798-804.
	Wyllie A, Kerr J, Currie A (1980) Cell Death: The Significance of Apoptosis. <i>Int. Rev. Cytol.</i> , 68: 251-306
	Xia Z, Dickens M, Raingeaud J, Davis RJ, Greenberg ME (1995). Opposing effects of ERK and JNK-p38 MAP kinases on apoptosis. <i>Science</i> 270: 1326-1331.
	Xing, R. et al., "Control of Breast Tumor Cell Growth Using a Targeted Cysteine Protease Inhibitor," <i>Cancer Res.</i> , Vol. 58, pp. 904-909 (1998)
	Yan S, Sameni M. and Sloane BF (1998). Cathepsin B and human tumor progression. <i>Biol Chem</i> 379: 113-123.
	Zhu D-M, Fang W-H, Nara R-K, and Uckun FM (1999). A requirement for protein kinase C inhibition for calcium-triggered apoptosis in Acute lymphoblastic leukemia cells. <i>Clin Can Res</i> 5: 355-360.
	Zhu, D.-M. and Uckun, F.M. (2000) "Z-Phe-Gly-NHO-Bz, an Inhibitor of Cysteine Cathepsins, Induces Apoptosis in Human Cancer Cells". <i>Clinical Cancer Research</i> , 6:2064-2069.
	Zhu, D.-M. and Uckun, F.M. (2000) "Cathepsin Inhibition Induces Apoptotic Death in Human Leukemia and Lymphoma Cells". <i>Leukemia and Lymphoma</i> , 39:343-354.
	Zuo H, Henzel WJ, Liu X, Lutschg A, Wang X (1997). Apaf-1, a human protein homologous to C. elegans CED-4, participates in cytochrome c-dependent activation of caspase-3. <i>Cell</i> 90: 405-413.

EXAMINER	DATE CONSIDERED	23552 PATENT TRADEMARK OFFICE
EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form for next communication to the Applicant.		